

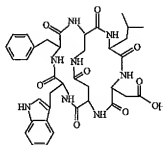
# Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application.

## Listing of Claims:

- (Withdrawn) Process for preparing bicyclic peptide compounds of formula (I)

Cyclo(Asp(OH)-Asp-Trp-Phe-Dpr-Leu)



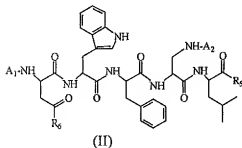
(I)

comprising the following steps:

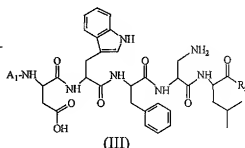
- deprotection of the linear pentapeptide of formula (II) in the presence of a solvent to give the compound of formula (III):

A<sub>1</sub>-Asp(R<sub>6</sub>)-Trp-Phe-Dpr(A<sub>2</sub>)-Leu-R<sub>5</sub>

A<sub>1</sub>-Asp(OH)-Trp-Phe-Dpr(H)-Leu-R<sub>5</sub>



(II)

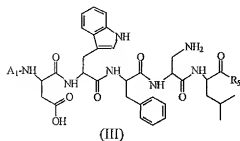


(III)

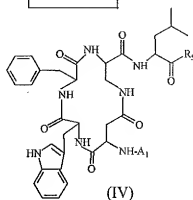
wherein A<sub>1</sub> and A<sub>2</sub> are two nitrogen protecting groups different from each other, and R<sub>5</sub> and R<sub>6</sub>, different from each other, are chosen from benzyloxy and lower alkyloxy groups in which the alkyl part comprises a linear or branched C1-C4 group;

- intramolecular cyclisation of the compound of formula (III) coming from step 1) in the presence of a solvent and of a suitable coupling agent to give the compound of formula (IV)

A<sub>1</sub>-Asp(OH)-Trp-Phe-Dpr(H)-Leu-R<sub>5</sub>



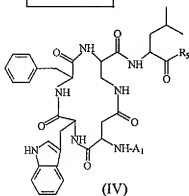
A<sub>1</sub>-Asp-Trp-Phe-Dpr-Leu-R<sub>5</sub>



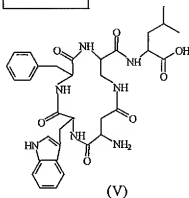
wherein R<sub>5</sub> is as defined above;

3) deprotection of the compound of formula (IV) coming from step 2) in the presence of a solvent to give the compound of formula (V)

A<sub>1</sub>-Asp-Trp-Phe-Dpr-Leu-R<sub>5</sub>

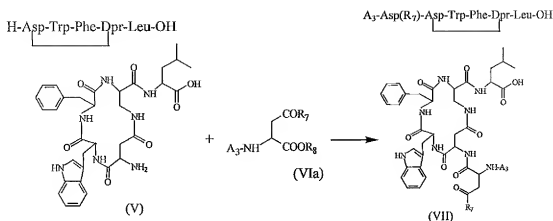


H-Asp-Trp-Phe-Dpr-Leu-OH



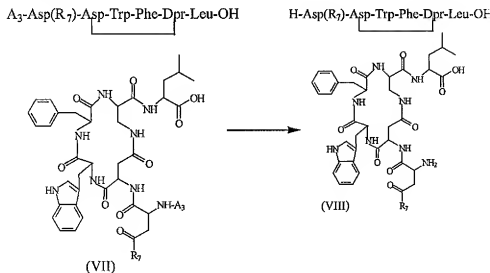
wherein R<sub>5</sub> is as defined above;

4) coupling between the compound of formula (V) coming from step 3) and a protected amino-acid of formula (VIa) in the presence of a solvent, to give compounds of formula (VII)



wherein A<sub>3</sub> is a nitrogen protecting group; R<sub>7</sub> is chosen from benzyloxy and lower alkyloxy groups, in which the alkyl part comprises a linear or branched C1-C4 group; R<sub>8</sub> is a residual group deriving from an activation procedure on the carboxyl group;

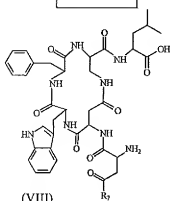
5) deprotection of the compound of formula (VII) coming from step 4) in the presence of a solvent to give a compound of formula (VIII)



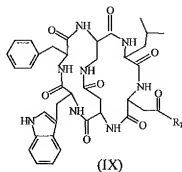
wherein R<sub>7</sub> is as defined above;

6) intramolecular cyclisation, in the presence of a solvent and of a suitable coupling agent, of the compound of formula (VIII) coming from step 5) to give a bicyclic compound of formula (IX)

H-Asp(R<sub>7</sub>)-Asp-Trp-Phe-Dpr-Leu-OH



Ciclo(Asp(R<sub>7</sub>)-Asp-Trp-Phe-Dpr-Leu)

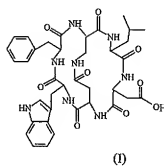
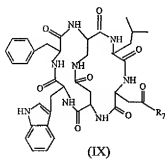


wherein R<sub>7</sub> is as defined above;

7) deprotection of the bicyclic compound of formula (IX) coming from step 6) in the presence of a solvent, to obtain the compound of formula (I)

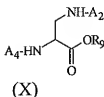
Ciclo(Asp(R<sub>7</sub>)-Asp-Trp-Phe-Dpr-Leu)

Cyclo(Asp(OH)-Asp-Trp-Phe-Dpr-Leu



wherein R<sub>7</sub> is as defined above.

2. (Withdrawn) The process according to claim 1, wherein the linear peptides of formula (II) are obtained by means of a sequential coupling strategy of suitable amino acids starting from a derivative of the amino acid Dpr of formula (X), protected on nitrogen and prepared separately or generated *in situ*



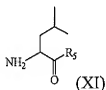
wherein

A<sub>2</sub> and A<sub>4</sub>, different from each other, are nitrogen protecting groups;

R<sub>9</sub> is a residual group deriving from an activation procedure, preferably chosen from the group consisting of benzyloxycarbonyl, alkoxycarbonyl comprising a linear or branched C1-C4 group in the alkyl part, and succinimidyl;

according to the following steps:

- reaction of the derivative of formula (X) above reported in the presence of a solvent with a Leu ester of formula (XI)



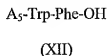
wherein R<sub>5</sub> is defined as in claim 1, to obtain the dipeptide A<sub>4</sub>-Dpr(A<sub>2</sub>)-Leu-R<sub>5</sub>,

- deprotection of the dipeptide A<sub>4</sub>-Dpr(A<sub>2</sub>)-Leu-R<sub>5</sub>, to obtain the monodeprotected dipeptide H-Dpr(A<sub>2</sub>)-Leu-R<sub>5</sub>;

- coupling the monodeprotected dipeptide H-Dpr(A<sub>2</sub>)-Leu-R<sub>5</sub> with the activated ester of the subsequent amino acid Phe and then successively with Trp and Asp, until the compounds of formula (II) are obtained.

3. (Withdrawn) The process according to claim 2, wherein the linear peptides of formula (II) are obtained by means of a synthesis strategy comprising the following steps:

- coupling of the monodeprotected dipeptide H-Dpr(A<sub>2</sub>)-Leu-R<sub>5</sub>, obtained as described in claim 2, with an activated derivative of the dipeptide of the following formula (XII)

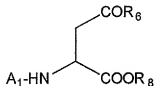


wherein A<sub>2</sub> and A<sub>5</sub>, different from each other, are nitrogen protecting groups,

prepared separately or generated *in situ* by coupling an activated ester of a Trp protected on nitrogen prepared separately or generated *in situ*, with a Phe ester and subsequent hydrolysis of the ester group, to obtain the tetrapeptide A<sub>5</sub>-Trp-Phe-Dpr(A<sub>2</sub>)-Leu-R<sub>5</sub>;

- suitable deprotection of the tetrapeptide A<sub>5</sub>-Trp-Phe-Dpr(A<sub>2</sub>)-Leu-R<sub>5</sub> from the group attached to the nitrogen of Trp;

- coupling of the deprotected tetrapeptide with a compound of formula (VI b)

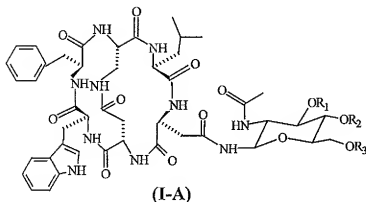


(VI b)

wherein A<sub>1</sub>, R<sub>6</sub> and R<sub>8</sub> are defined as in claim 1.

4. (Withdrawn) The process according to claim 2, wherein the linear peptides of formula (II) are obtained by means of a synthesis strategy of the 3+2 type that involves coupling the tripeptide A<sub>1</sub>-Asp(R<sub>6</sub>)-Trp-Phe-OH, obtained by removing the nitrogen protecting group from the compounds of formula (XII) above reported, subsequent coupling with a compound of formula (VIb) above reported and then further coupling with the monodeprotected dipeptide H-Dpr-(A<sub>2</sub>)-Leu-R<sub>5</sub> prepared as described in claim 2.

5. (Withdrawn) The process according to claim 1, wherein said nitrogen protecting groups are selected from the group consisting of benzyloxycarbonyl and alkoxy carbonyls in which the alkyl part comprises a linear or branched C1-C4 group.
6. (Withdrawn) The process according to claim 5, wherein said nitrogen protecting groups are selected from t-butoxycarbonyl and benzyloxycarbonyl.
7. (Withdrawn) The process according to claim 1, wherein said  $R_8$  group is selected from the group consisting of benzyloxycarbonyl, alkyloxycarbonyl comprising a linear or branched C1-C4 group in the alkyl part, succinimidyl, benzotriazole possibly substituted by a halogen and azabenzotriazole.
8. (Withdrawn) The process according to claim 1, wherein said linear or branched C1-C4 group is selected from the group consisting of methyl, ethyl, propyl, butyl, isopropyl and t-butyl.
9. (Currently amended) A process for preparing a bicyclic glycopeptide compound of formula (I-A)

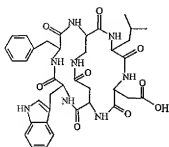


wherein  $R_1$ ,  $R_2$  and  $R_3$ , equal or different from each other, can be hydrogen or an oxygen protecting group, selected from the group consisting of -COR<sub>4</sub> wherein  $R_4$  is selected from the group consisting of a linear or branched C1-C4 alkyl group, phenyl and phenyl substituted with a halogen atom, benzyl or benzoyl, comprising the following steps:

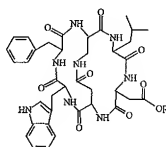
1A) activation of the bicyclic peptide compounds of formula (I) with a suitable coupling agent selected from the group consisting of isobutyl chloroformate, a carbodiimide and a carbodiimide in combination with a hydroxy containing compound, phosphonium salts, N-oxide guanadine salts or uronium salts of to obtain a derivative of formula (II-A)

Ciclo(Asp(OH)-Asp-Trp-Phe-Dpr-Leu)

Ciclo(Asp(OR)-Asp-Trp-Phe-Dpr-Leu)



(I)

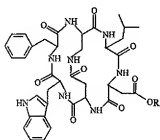


(II-A)

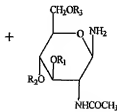
wherein R is a member group selected from the group consisting of benzotriazole, substituted with a halogen possibly azabenzotriazole, succinimidyl and benzotriazole substituted with halogen;

;

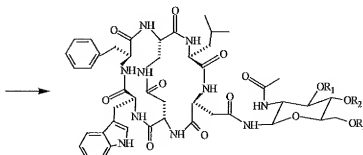
Ciclo(Asp(OR)-Asp-Trp-Phe-Dpr-Leu)



(II-A)



(III-A)



(I-A)



2A) reaction of the compound of formula (II-A) deriving from step 1A) in the presence of a solvent with the glycosidic derivative of formula (III-A)

wherein R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> are defined as above.

10. (Previously Presented) The process according to claim 9, wherein the compounds of formula (I-A) wherein R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are different from H, are transformed into the corresponding compounds of formula (I-A) wherein R<sub>1</sub>=R<sub>2</sub>=R<sub>3</sub>=H, by a deprotection reaction in the presence of a solvent.

11. (Cancelled)

12. (Currently Amended) The process according to claim ~~11~~ 9, wherein said C1-C4 alkyl group is selected from the group consisting of methyl, ethyl, propyl, butyl, isopropyl and t-butyl.

13. (Previously Presented) The process according to claim 12, wherein said C1-C4 alkyl group is methyl.

14. (Previously Presented) The process according to claim 9, wherein said glycosidic derivatives of formula (III-A) are selected from the group consisting of 2-acetamide-2-deoxy- $\beta$ -D-glucopyranosylamine and 2-acetamide-3,4,6-tri-O-acetyl-2-deoxy- $\beta$ -D-glucopyranosylamine.

15. (Cancelled)

16. (Withdrawn) The process in combination according to claim 1, wherein said coupling agent is selected from the group consisting of isobutyl chloroformate, a carbodiimide possibly in combination with a hydroxy derivative, phosphonium salts, N-oxide guanidine salts or uronium salts.

17. (Withdrawn) The process Process according to claim 16, wherein said carbodiimides are selected from dicyclohexylcarbodiimide and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride; said hydroxy derivative is selected from 1-hydroxybenzotriazole, 6-chloro-1-hydroxybenzotriazole, hydroxysuccinimide and 1-

hydroxy-7-azabenzotriazole; said phosphonium salts, N-oxide guanidine salts and uronium salts are selected from (Benzotriazol-1-yloxy)tri(dimethylamino)phosphonium hexafluorophosphate, (Benzotriazol-1-yloxy)tripyrrolidine phosphonium hexafluorophosphate, 1-[bis(dimethylamino)methylene]-1H-benzotriazolium-3-oxide hexafluorophosphate, 1-[bis(dimethylamino)methylene]-5-chloro-1H-benzotriazolium-3-oxide hexafluorophosphate, 1-[bis(dimethylamino)methylene]-1H-benzotriazolium-3-oxide tetrafluoroborate, 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazole[4,5-b]pyridinium-3-oxide hexafluorophosphate, 1-[bis(dimethylamino)methylene]-5-chloro-1H-benzotriazolium-3-oxide tetrafluoroborate, O-[(ethoxycarbonyl)cyanomethylenamino]-N,N,N',N'-tetramethyluronium tetrafluoroborate, O-(bicyclo[2.2.1]hept-5-ene-2,3-dicarboximido)-N,N,N',N'-tetramethyluronium tetrafluoroborate, and O-(N-succinimidyl)-N,N,N',N'-tetramethyluronium tetrafluoroborate.

18. (Withdrawn) The process according to claim 1, wherein said coupling reactions are carried out in the presence of a tertiary amine in an organic solvent at a temperature comprised between -20 and +50°C.

19. (Withdrawn) The process according to claim 18, wherein said tertiary amine is selected from the group consisting of N-methylmorpholine, triethylamine and diisopropylethylamine, and said organic solvent is selected from the group consisting of ethyl acetate, dimethylformamide and N-methylpyrrolidone.

20. (Withdrawn) The process according to claim 1, wherein said deprotection reactions are carried out by means of hydrogenation in the presence of a catalyst in a solvent selected from solvents which dissolve the components of the reaction without reacting with them, excluding ketones and solvents which poison the catalyst, at a temperature comprised between -20 and +50°C.

21. (Withdrawn) The process according to claim 20, wherein said catalyst is selected from 5% and 10% Palladium and said solvent is selected from dimethylformamide, N-methylpyrrolidone, acetic acid, p-toluenesulfonic acid, methanol, ethanol, isopropanol, and mixtures thereof.

22. (Withdrawn) The process according to claim 1, wherein said deprotection reactions are carried out by means of acid treatment with pure acids or with acids mixed with other solvents, at a temperature comprised between -20 and +50°C.
23. (Withdrawn) The process according to claim 22, wherein said acids are selected from hydrochloric acid, trifluoroacetic acid and formic acid.
24. (Withdrawn) The process according to claim 1, wherein said deprotection reactions are carried out by means of treatment with a base compound in the presence of a solvent, at a temperature comprised between -20 and +50°C.
25. (Withdrawn) The process according to claim 24, wherein said base compound is selected from hydroxides of alkali metals or alkaline earth metals, and said solvent is selected from the group consisting of water, dioxane, acetonitrile, methanol, ethanol, isopropanol, and mixtures thereof.
26. (Currently Amended) The process according to claim 9, wherein said coupling agent is selected from the group consisting of isobutyl chloroformate, a carbodiimide and a carbodiimide possibly in combination with a hydroxy derivative containing compound, phosphonium salts, N-oxide guanidine salts and or uronium salts.
27. (Previously Presented) The process according to claim 26, wherein said carbodiimides are selected from dicyclohexylcarbodiimide and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride; said hydroxy derivative is selected from 1-hydroxybenzotriazole, 6-chloro-1-hydroxybenzotriazole, hydroxysuccinimide and 1-hydroxy-7-azabenzotriazole; said phosphonium salts, N-oxide guanidine salts and uronium salts are selected from (Benzotriazol-1-yloxy)tri(dimethylamino)phosphonium hexafluorophosphate, (Benzotriazol-1-yloxy)tripyrrolidine phosphonium hexafluorophosphate, 1-[bis(dimethylamino)methylene]-1H-benzotriazolium-3-oxide hexafluorophosphate, 1-[bis(dimethylamino)methylene]-5-chloro-1H-benzotriazolium-3-oxide hexafluorophosphate, 1-[bis(dimethylamino)methylene]-1H-benzotriazolium-3-oxide tetrafluoroborate, 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazole[4,5-b]pyridinium-3-oxide hexafluorophosphate, 1-[bis(dimethylamino)methylene]-5-chloro-1H-benzotriazolium-3-oxide tetrafluoroborate, O-[(ethoxycarbonyl)cyanomethylenamino]-N,N,N',N'-tetramethyluronium tetrafluoroborate, O-(bicyclo[2.2.1]hept-5-ene-2,3-

dicarboximido)-N,N,N',N'-tetramethyluronium tetrafluoroborate, and O-(N-succinimidyl)-N,N,N',N'-tetramethyluronium tetrafluoroborate.

28. (Previously Presented) The process according to claim 9, wherein said coupling reactions are carried out in the presence of a tertiary amine in an organic solvent at a temperature comprised between -20 and +50°C.

29. (Previously Presented) The process according to claim 28, wherein said tertiary amine is selected from the group consisting of N-methylmorpholine, triethylamine and diisopropylethylamine, and said organic solvent is selected from the group consisting of ethyl acetate, dimethylformamide and N-methylpyrrolidone.

30. (Currently Amended) The process according to claim 10, wherein said deprotection reactions are carried out by ~~means of~~ hydrogenation in the presence of a catalyst in a solvent selected from solvents which dissolve the components of the reaction without reacting with them, excluding ketones and solvents which poison the catalyst, at a temperature comprised between -20 and +50°C.

31. (Previously Presented) The process according to claim 30, wherein said catalyst is selected from 5% and 10% Palladium and said solvent is selected from dimethylformamide, N-methylpyrrolidone, acetic acid, p-toluenesulfonic acid, methanol, ethanol, isopropanol, and mixtures thereof.

32. (Previously Presented) The process according to claim 10, wherein said deprotection reactions are carried out by means of acid treatment with pure acids or with acids mixed with other solvents, at a temperature comprised between -20 and +50°C.

33. (New) The process according to claim 32, wherein said acids are selected from hydrochloric acid, trifluoroacetic acid and formic acid.

34. (New) The process according to claim 10, wherein said deprotection reactions are carried out by means of treatment with a base compound in the presence of a solvent, at a temperature comprised between -20 and +50°C.

35. (New) The process according to claim 34, wherein said base compound is selected from hydroxides of alkali metals or alkaline earth metals, and said solvent is selected from

the group consisting of water, dioxane, acetonitrile, methanol, ethanol, isopropanol, and mixtures thereof.